PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BP/G-33315A/BCK	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/009055	International filing date *(day/month/year)* 12.08.2004	Priority date *(day/month/year)* 13.08.2003
International Patent Classification (IPC) or national classification and IPC C12P21/00, C07K14/56		
Applicant SANDOZ AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand 21.06.2005	Date of completion of this report 15.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Schneider, P Telephone No. +31 70 340-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/EP2004/009055

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-25 as originally filed

   Claims, Numbers

   1-23 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/009055

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 13,20-23 (all completely),14-19 (all partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 13,20-23 (all completely),14-19 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/009055

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-12 (all completely),14-19 (all partially) .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12 (all completely),14-19 (all partially)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-12 (all completely),14-19 (all partially)
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-12 (all completely),14-19 (all partially)
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item IV.

Lack of unity of invention

The separate inventions/groups of inventions are:

1-12 (all completely),14-19 (all partially)
A process to release a recombinant polypeptide of interest from the periplasm of the host cells by applying an osmotic shock directly on the host cells in the fermentation medium.

13,20-23 (all completely),14-19 (all partially)
A process for the purification of a recombinant interferon alpha 2 from a crude preparation of interferon alpha 2 by applying a specific sequence of several chromatographic steps as defined in claim 13 (i) to (v).

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The subject matter of independant claim 1 is a process to release a recombinant polypeptide of interest from the periplasm of the host cells by applying an osmotic shock directly on the host cells in the fermentation medium. The problem to be solved is the provision of a simplified method to extract polypeptides from the periplasm of fermented procaryotes.
The subject matter of independant claim 13 is a process for the purification of a recombinant interferon alpha 2 from a crude preparation of interferon alpha 2 by applying a specific sequence of several chromatographic steps as defined in claim 13 (i) to (v). The problem to be solved is the provision of a simplified method to purify interferon alpha 2.
The present set of claims solves two different, independant technical problems, which were known in the prior art. No technical relationship can be identified between the solutions to both problems, i.e. both solutions can be used independently from each other, their functioning does not depend on each other. Two different solutions to two different, known problems were put in a row. Additionally, independant claims 1 and 13 do not share a common matter. Therefore, they form different inventions.

As a consequence, the ISA is of the opinion that there is no single inventive concept

underlying the plurality of claimed inventions of the present application in the sense of rule 13.1 PCT. Consequently there is lack of unity and the different inventions, which are directed to the two above-mentioned technical problems, not belonging to a common inventive concept, are formulated as the different subjects on the communication pursuant to Art. 17(3)(a) PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: HART R A ET AL.: BIOTECHNOLOGY, NATURE PUBLISHING CO. NEW YORK, US, vol. 12, November 1994 (1994-11), pages 1113-1117, ISSN: 0733-222X

1 Novelty (Art. 33(2) PCT)

The subject matter of claims 1 to 12 and 14 to 19 (as far as applicable) is a process to release a recombinant polypeptide of interest from the periplasm of the host cells by applying an osmotic shock directly on the host cells in the fermentation medium. Such a method has not been disclosed in the prior art. Therefore, the subject matter of claims 1 to 12 and 14 to 19 (as far as applicable) are novel under Art. 33(2) PCT.

2 Inventive Step (Art. 33(3) PCT)

D1 is the closest prior art and discloses the release of periplasmic IGF-I into the fermentation medium using chaotrope and reductant (urea, DTT, eachl + NaOH, see abstract), from which the subject matter of the present application differs in that the release of the periplasmic protein is achieved by an osmotic shock. No technical effect can be seen that is caused by said difference. The problem to be solved is the provision of an

alternative method to release the periplasmic protein of interest into the fermentation medium.
No hint can be identified in the prior art to apply an osmotic shock directly on cells in the fermentation broth. All osmotic shocks in the prior art were applied on harvested cell which were separated from the fermentation broth. The solution of the present application has the advantage that said harvesting step is not necessary and the whole procedure is simplified. Therefore, the present application involves an inventive step under Art. 33(3) PCT.

4 Industrial Application (Art. 33(4) PCT)

The present claims fulfill the requirement of industrial applicability (Art. 33(4) PCT).

5 Clarity (Art. 6 PCT)

Claims 1, 2, 14 and 15 attempt to define the subject matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added (Guidelines 5.35).